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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/657,550	CHAUDRY, IMTIAZ	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 3-6, 10-15, 22-25, 27-30, 35, 71-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,10-15,22-25,27-30,35 and 71-76* is/are rejected.

7)☒ Claim(s) *71-75* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-6, 10-15, 23-25, 27-30, 35, and 71-76 are pending. Applicant previously cancelled claim 26. Applicant has newly cancelled claims 2, 7-9, 16-21, 31-34, and 36-70. Applicant has amended claims 1, 3, 71, and 73. Claims 75-76 are new. Receipt and consideration of Applicant's amended claim set, new IDS (submitted 2/29/2008), and remarks/arguments submitted on May 2, 2007 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2 May 2008 has been entered.

Moot Rejections/objections

All rejections and/or objections of claims 2, 7-9, 16-21, 31-34, and 36-70 cited in the previous office action mailed on December 5, 2007 **are moot**, because said claims have been cancelled.

Election/Restrictions

Although Applicant has cancelled all previously withdrawn claims (i.e. claims 2, 7-9, 16-21, 31-34, and 36-44, which were withdrawn as being drawn to a non-elected species and claims

45-70, which were withdrawn as being drawn to a non-elected invention), the election/restriction of record remains proper and is maintained at this time.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claims 71-75 are objected to because of the following informalities: (1) the word cidofovir is misspelled on line 5 of claim 75 as "cidovir"; and (2) the word "edetate" is misspelled on line 3 of claims 71 and 73, on line 2 of claims 72 and 74 as "edentate". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 10-15, 22-25, and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Determination of Claim Scope

Claim 1 of the instant application claims a formulation comprising (a) an aqueous suspension of a solid anti-inflammatory steroid characterized by a particular particle size distribution and (b) an antifungal agent in a particular amount, wherein the anti-inflammatory steroid is fluticasone or pharmaceutically acceptable salts, esters, enol ethers, enol esters, acids, bases, **solvates, or hydrates thereof**.

Review of Applicants' Disclosure

The instant specification does not disclose, to which solvates or hydrates of fluticasone, mometasone, or beclomethasone Applicants are referring. Applicants' specification does not disclose how to make any particular solvate or hydrate of fluticasone nor does Applicant depict chemical structures of fluticasone as any particular hydrate or solvate in their disclosure.

Possession Based on Ordinary Skilled Artisan's Determination/ State of the Prior Art

A search of the prior art did not uncover any known solvates or hydrates of fluticasone. It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 18), therefore, the generic reference to a solvate of either [specify species] in the instant specification does not provide adequate written support

for claims drawn to any solvate or hydrate of these compounds. An ordinary skilled artisan would conclude that Applicants were not in possession of compositions comprising any particular solvate or hydrate of fluticasone, mometasone, or beclomethasone. Furthermore, because Applicants' generic reference to solvates or hydrates of fluticasone, mometasone, or beclomethasone does not permit the ordinary skilled artisan to clearly envisage what specific solvates and/or hydrates of fluticasone were in Applicants' possession, the only reasonable conclusion said artisan would make was that Applicants were not in possession of the genus of all known and unknown solvates and/or hydrates of fluticasone and had not reduced to practice the preparation, isolation, and characterization of said solvates and hydrates.

The remaining claims are rejected as depending from a rejected claim.

Claims 1, 3-6, 10-15, 22-25, and 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions wherein the anti-inflammatory steroid is fluticasone or pharmaceutically acceptable salts, esters, enol ethers, enol esters, acids, bases thereof, it does not reasonably provide enablement for compositions comprising solvates or hydrates of fluticasone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997);

In re Wright 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad with regards to the subgenera of pharmaceutically acceptable salts, esters, enol ethers, enol esters, acids, bases, solvates, or hydrates of fluticasone.

Nature of the invention/State of the Prior Art

Claim 1 of the instant application claim a formulation comprising (a) an aqueous suspension of a solid anti-inflammatory steroid characterized by a particular particle size distribution and (b) an antifungal agent in a particular amount, wherein the anti-inflammatory steroid is fluticasone or pharmaceutically acceptable salts, esters, enol ethers, enol esters, acids, bases, **solvates, or hydrates thereof**. It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 11 and 18). A search of the prior art did not uncover any known solvates or hydrates of fluticasone.

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970). The art is especially unpredictable with regards to the existence and formation of particular polymorphs and pseudopolymorphs (e.g. hydrates and solvates) of chemical compounds, as set forth above by the teachings of Vippagunta et al.

Guidance/Working Examples

Applicants provide no guidance or working examples about the preparation of any solvate or hydrate of any of fluticasone.

In conclusion, the specification, while being enabling for compositions as described above wherein the anti-inflammatory steroid is fluticasone or pharmaceutically acceptable salts, esters, enol ethers, enol esters, acids, bases thereof, it does not reasonably provide enablement for compositions comprising solvates or hydrates of fluticasone.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 75-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 75 is vague, because it is unclear what are the metes and bounds of the Markush group of antiviral agents in said claim which is described using intermediate claim langauge (i.e.

"consisting essentially of"). The phrase "consisting essentially of" is not closed, and, because it is not closed it allows for the possibility of other components of the recited Markush group, such that an ordinary skilled artisan would not be apprised of the metes and bounds of said Markush group. Applicant is kindly requested to utilize proper Markush group language. See MPEP 2111.03 [R-3].

Claim 76 is vague and indefinite, because it is unclear what antiviral is being described. Description of an antiviral agent as "comprising" edoxudine merely describes a portion of the antiviral agent (i.e. a single molecular entity), thus, an ordinary skilled artisan would not be apprised of whether the antiviral agent is a molecule with an edoxudine moiety in addition to other structural components. An alternative interpretation would be that Applicant intended the term "antiviral agent" to refer to a mixture of components.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.

3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 10-15, 22-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp 26-28, 225-226, 445-446, 453-456, and 721-722)[1] in view of Bernini et al. (U.S. Patent No. 6,464,958).

Applicant Claims

Applicant claims a formulation comprising (a) 1-700 micrograms of a steroidal anti-inflammatory that is fluticasone or an acceptable derivative thereof characterized by the particle size distribution described in claim 1, further comprising (b) a preservative, such as benzalkonium chloride (e.g. claims 23-24 and 28) and (c) other excipients (e.g. dextrose, carboxymethylcellulose sodium, etc.).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Bernini were set forth in the office action mailed on April 23, 2007. FLONASE® is a commercially available nasal spray sold in a metering, atomizing, spray pump containing therein an aqueous suspension of suspended microfine fluticasone propionate (16 g

[1] The following pages of the 1999 edition of the DIH are already of record: 445-446.

bottle delivering 120 individual 50 microgram doses per actuation; i.e. **0.0375% w/w fluticasone propionate**), **microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, 0.25% w/w phenylethyl alcohol, wherein the aqueous suspension has a pH between 5 and 7** (PDR printout, pg. 1, "Description section"). The recommended dosage of FLONASE® for adults is 50 micrograms per nostril for a total **daily dosage of 200 micrograms**. Alternatively, the administration of two 100 microgram doses twice daily is also effective. Adolescents and children 4 years of age and older should begin with **100 microgram dosages** (1 spray per nostril per day), but may use 200 micrograms (2 sprays per nostril per day) if not adequately responding (PDR, pg. 7, "Dosage and Administration" section). The DIH demonstrates that FLONASE® was a commercially available product at least as early as 1999. The DIH also sets forth that **neomycin sulfate** (pg. 721-722) was a known antibiotic at the time of Applicant's invention and that **acyclovir** (pgs. 26-28), **ganiciclovir** (pgs. 463-464), **foscarnet** (pgs. 454-456), **cidofovir** (pgs. 225-226), and **formivirsen** (pgs. 453-454) were all known antiviral agents at the time of Applicant's invention.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

The product information concerning FLONASE® is silent as to the particle size distribution of suspended beclomethasone. The product size distribution is either inherent to FLONASE® or it is obviated by the teachings of Bernini as further articulated below.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It is incumbent on Applicant to demonstrate that the particle size distribution of the suspended fluticasone propionate of FLONASE® is not the same or substantially similar to that claimed by Applicant. It is noted that Applicant has indicated in the specification that there is no statistical difference between high dose formulations of FLONASE® and Applicant's high dose formulation. However, it is unclear what constitutes a "high dose" of Applicant's formulation and FLONASE®, per Applicant's statement. Applicant's data in Figure 1, for example, also strongly supports the notion that FLONASE® is the same or substantially similar to Applicant's claimed composition, because Applicant's data compared to FLONASE® exhibit the same pattern of fluctuations over a period of 2-14 days; is of a similar magnitude, and in several instances is the same or essentially the same (see, for example, data points at 4, 10, 11, and 13 days). Furthermore, the general differences depicted in Figures 1-4 appear to be merely a difference of degree at best and not a difference of kind. A difference of degree is not sufficient to support patentability. It is noted that Applicant admitted in paragraph 86 of the specification of copending application 10/414,682, which Applicants have incorporated by reference in the instant application, that there was no statistically significant differences between Dey-FP (Applicant's invented composition) and FLONASE® High and Low Dose groups for any efficacy endpoint analysis (relief of signs and symptoms of SAR).

Nonetheless, even if Applicant can demonstrate that the particle size distribution of fluticasone propionate in the claimed composition is not the same as the particle size distribution characterizing the suspended fluticasone propionate of FLONASE®, it would have been prima facie obvious to a person of ordinary skill to modify the particle size distribution of a composition comprising beclomethasone, because it is well known in the art that the particle size

distribution of an aerosolized drug composition is very important to the therapeutic efficacy of the drug when delivered by inhalation. It is noted that Bernini teaches aqueous suspensions of beclomethasone having particle size distributions very similar to the particles size distributions of BDP particles in aqueous suspensions claimed by Applicants The physical characteristics (e.g. size and shape) of particulate compositions are clearly result specific parameters that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal physical particle characteristics (e.g. particle size and/or particle size distribution) of a particulate composition needed to achieve the desired results. It is noted that Bernini stated that suspensions treated with a high-pressure homogenizer (See Example 6) were characterized by remarkably improved nebulization performance. Thus, an ordinary skilled artisan would have been motivated to obtain particles having distributions, such as those taught by Bernini in Table 7 of Example 6, for nebulization to the nasal mucosa, because said suspensions exhibited remarkable nebulization performances and an ordinary skilled artisan would have been able to utilize Bernini's teachings to obtain various particle size distributions with a reasonable expectation of success. Regarding the amounts of suspended steroid, the prior art clearly recognizes that one can increase the dosage of fluticasone or another anti-inflammatory steroid as is necessary to treat a given patient's symptoms. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Therefore, the claimed invention, as a whole, would have been *prima facie*

obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 5/2/08 have been fully considered but they are not persuasive. Applicants' have traversed the instant rejection by arguing that (1) Bernini allegedly teaches away from the claimed invention due to the statement in column 1, lines 33-38 directed towards MMAD sizes greater than 5-6 microns are needed for nasal administration; (2) Bernini is silent regarding treatment of rhinitis and/or any symptoms of rhinitis; and (3) Bernini is allegedly flawed because Bernini's teachings are not anticipatory of Applicants' claims reciting a specific particle size distribution; (4) the ordinary skilled artisan would allegedly have not motivation and reasonable expectation of success upon modifying the teachings of FLONASE® per the teachings of Bernini.

The Examiner respectfully disagrees with Applicants' traversal arguments. Firstly, regarding Applicants traversal of the instant rejection by attacking solely the Bernini reference, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The combined prior art references contemplate the treatment of rhinitis by the nasal administration of an aqueous suspension of an anti-inflammatory corticosteroid (i.e. fluticasone or beclomethasone, which is interchangeable with fluticasone). Regarding Applicants' assertion that there is no reasonable expectation of success upon modification of FLONASE® per the

teachings of Bernini, Applicants have provided no credible scientific or technical reason demonstrating why an ordinary skilled artisan would doubt that FLONASE® could be modified by the teachings of Bernini. Furthermore, although Bernini does have a statement about MMAD for nasal administration being greater than 5-6 microns, this range would necessarily overlap with Applicants' broadest claims. It has already been established that optimization of particle sizes is routine in the field of inhalable formulations (i.e. both oral and nasally administered). Thus, finding the optimal particle size and particle size distribution for a given particulate formulation is routinely practiced in the art and as applied to the combined prior art, would reasonably be expected to yield the same or a substantially similar particle size distribution as claimed by Applicants. Regarding Applicants' data it is clear that the performance of both high and low-dose FLONASE® vis-à-vis the high and low dose formulations of Applicants' invention result in clinically comparable and in some cases indistinguishable results (see for example data points in Applicants' figure 1 at days 7, 10, and 12-14). Contrary to Applicants' statements, Applicants' results when taken as a whole and compared to the results exhibited by FLONASE® are not considered to demonstrate anything surprising or unexpected, as has been explained in previous office actions. Thus, Applicants' formulations are not considered to exhibit unexpected are surprising results either. The instant rejection remains proper and is maintained.

Claims 3-6, 29-30, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp 445-446) in view of

Bernini et al. (U.S. Patent No. 6,464,958) as applied to claims 1, 10-15, 22-25, and 27-28 above, and further in view of Osbakken et al. (US 2002/0061281).

Applicant Claims

Applicant claims a formulation as described above in the instant application further comprising about 0.5 to about 150 mg of an anti-fungal agent (e.g. amphotericin beta) or an antibiotic (e.g. doxycycline).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE®, the PDR®, and the DIH were set forth above in the instant office action. The teachings of Bernini and Osbakken were set forth on pages 6-9 (Osbakken) and 12-13 (Bernini) of the office action mailed on April 23, 2007.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

FLONASE® lacks the teaching of further comprising an antifungal agent or an antibiotic. This deficiency is cured by the teachings of Osbakken, which has been provided as a supporting document to show what was known in the art regarding the treatment of rhinitis/sinusitis.

Finding of Prima Facie Obviousness Rational and Motivation ***(MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to modify the compositions of FLONASE®/Bernini with the teachings of

Osbakken, because it was well-known at the time of the instant invention that sinusitis is a species of rhinosinusitis (i.e. rhinitis) and is an inflammation of one or more membranes of the paranasal sinuses (i.e. paranasal mucosae) can be caused by microbial infection (i.e. fungal or bacterial infection). Using common sense and what was readily known to the ordinary skilled artisan at the time of the instant invention, one would have recognized that the underlying cause of sinusitis or rhinitis could be treated by the inclusion of an anti-microbial agent, such as an anti-fungal agent (e.g. amphotericin beta) or an antibacterial (e.g. doxycycline) in a therapeutically effective dosage. Thus, despite the fact that Osbakken focuses its teachings on aqueous solutions that are filtered, an ordinary skilled artisan would nonetheless have been motivated to modify FLONASE® to incorporate a therapeutically effective amount of an anti-fungal agent and/or an antibacterial to obtain a composition suitable for treating not only the inflammation resulting from an infection, but also suitable for treating the underlying cause of the inflammation (i.e. a fungal and/or bacterial infection). An ordinary skilled artisan would have had a reasonable expectation of success upon modification of the FLONASE®/Bernini composition to further comprise an anti-fungal or antibacterial agent because these are art-recognized therapeutics for treating fungal and bacterial infections and are known in combination with anti-inflammatory steroids. Regarding Applicant's allegation of unexpected results, the Examiner's position related to this allegation is the same as set forth above and is herein incorporated by reference. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 5/2/08 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by presenting the same and/or similar arguments as were rebutted in the previous rejection. Thus, the Office's rebuttal arguments are herein incorporated by reference. The rejection is considered to remain proper and is maintained.

Claims 71-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp 26-28, 225-226, 445-446, 453-456, and 721-722) in view of Bernini et al. (U.S. Patent No. 6,464,958) and Osbakken et al. (US 2002/0061281) as applied to claims 3-6, 29-30, and 35 above, and further in view of Doi (U.S. Patent No. 6,368,616) and Meade (U.S. Patent No. 6,608,054).

Applicant Claims

Applicant claims a formulation as described above in the instant application further comprising a complexing agent (e.g. sodium edetate)

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE®, the PDR®, and the DIH were set forth above in the instant office action. The teachings of Bernini and Osbakken were set forth on pages 6-9 (Osbakken) and 12-13 (Bernini) of the office action mailed on April 23, 2007. Doi teaches aqueous

suspensions for nasal application and that the compositions may contain additives which are broadly used in nasal drops, such as preservatives, buffers (e.g. **citric acid**), stabilizers, chelating agents (e.g. **citric acid and editic acid**), pH control agents (e.g. **citric acid**), etc. (title; abstract; col. 2, lines 61-65; col. 3, lines 8-17). The term "chelating agent" is synonymous with "complexing agent." Meade teaches that sodium edetate and citric acid are known complexing agents (col. 9, lines 22-34).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

FLONASE® lacks the teaching of compositions further comprising a complexing agent. This deficiency is cured by the teachings of Doi or Meade, which have been provided as supporting documents to show that complexing agents are conventional ingredients in aqueous nasal formulations.

Finding of Prima Facie Obviousness Rational and Motivation ***(MPEP §2142-2143)***

It would have been prima facie obvious to an ordinary skilled artisan at the time of the instant invention to modify the FLONASE®/Bernini/Osbakken compositions to further comprise a conventional additive broadly used in the formulation of nasal compositions, such as complexing agents. Regarding the specific complexing agent used, an ordinary skilled artisan would have been motivated to utilize any of the well-known complexing agents routinely utilized in aqueous nasal formulations (e.g. EDTA, sodium edetate, citric acid, etc.). An ordinary skilled artisan would have had a reasonable expectation of success, because the addition of complexing

agents to aqueous formulations (e.g. nasally administrable aqueous suspensions) is conventional in the art. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 5/2/08 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by presenting the same and/or similar arguments as were rebutted in the previous rejection. Thus, the Office's rebuttal arguments are herein incorporated by reference. The rejection is considered to remain proper and is maintained.

Claims 75-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp 26-28, 225-226, 445-446, 453-456, and 721-722), in view of Bernini et al. (U.S. Patent No. 6,464,958), Osbakken (US 2002/0061281), as applied to claims 1, 10-15, 22-25, and 27-28 above, and further in view of Walker ("Management of allergic rhinitis", *Nursing Times,* 2003, *99(23)*, Abstract) and Hamuy et al.("Topical antiviral agents for herpes simplex virus infections", *Drugs Today*, 1998, *34(12)*, Abstract Only).

Applicant Claims

Applicant claims a formulation as described above in the instant application that additionally comprises a therapeutic amount of an antiviral agent selected from a group consisting essentially of acyclovir, famciclovir, valacyclovir, edoxudine, ganciclovir, foscarnet, cidovir (vistide), vitrasert, and formivirsen, and in some embodiments further comprises a complexing agent (e.g. sodium edetate).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE, the PDR®, the DIH, Bernini, and Osbakken were restated above in the instant office action.

Walker teaches that viral and bacterial infection is the commonest acute cause of symptoms of allergic rhinitis (abstract).

Hamuy identifies several antiviral agents that have been used successfully to treat herpes simplex virus, including **cidofovir, edoxudine**, and penciclovir (abstract).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

FLONASE® lacks the teaching of compositions comprising an antiviral agent and an antibacterial agent. The antibacterial agent deficiency is cured by the teachings of Osbakken (see Table 1). The antiviral agent deficiency is cured by the teachings of Walker and Hamuy, which have been provided as supporting documents to demonstrate that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are well-known anti-viral agents (Hamuy).

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been prima facie obvious to an ordinary skilled artisan at the time of the instant invention to modify the FLONASE®/Bernini/Osbakken compositions to further comprise a known antiviral agent, such as cidofovir or edoxudine, because viral infections are known to play a role in the etiology of allergic rhinitis and cidofovir, edoxudine, acyclovir, ganiciclovir, foscarnet, and formivirsen are well-known antiviral agents. An ordinary skilled artisan would have had a reasonable expectation of success upon addition of a known antiviral agent, because viruses are known to play a role in the cause of acute allergic rhinitis and both cidofovir and edoxudine are known anti-viral agents. Regarding the particle size distributions recited in Applicant's claims, these have been addressed above in the previous rejections under 35 USC §103(a), and the relevant reasoning is incorporated herein by reference. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed May 5, 2008 as applied to the new rejection have been fully considered but they are not persuasive for the reasons set forth in the previous rejections under 35 USC §103(a).

Conclusion

Claims 1, 3-6, 10-15, 22-25, 27-30, 35, and 71-76 are rejected. Claims 71-75 are objected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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